Cannabidiol normalises medial temporal, midbrain and striatal dysfunction in people at clinical high-risk for psychosis

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KEY POINTS:

Question: What are the neurocognitive mechanisms that underlie the putative therapeutic effects of cannabidiol in psychosis?

Findings: We show that a single oral dose of cannabidiol modulated activation in the striatum, medial temporal cortex and midbrain in clinical high-risk (CHR) patients, such that in each of these regions, the level of activation following administration of cannabidiol to CHR patients was intermediate between that in healthy controls and in CHR patients under placebo.

Meaning: These results suggest that cannabidiol may normalize dysfunction in these brain regions, which are critically implicated in psychosis. This may underlie its therapeutic effects in psychosis.

ABSTRACT:

Importance: Cannabidiol (CBD) has antipsychotic effects in humans, but how these are mediated in the brain remains unclear.

Objective: To investigate the neurocognitive mechanisms that underlie the therapeutic effects of CBD in psychosis.

Design: Parallel-group, double-blind, randomized, placebo-controlled design in people at clinical high risk (CHR) for psychosis. Healthy control (HC) participants were studied under identical conditions without any drug treatment.

Setting: Academic Health Science Centre, UK

Participants: Thirty-three medication-naïve CHR and 19 HC participants.

Intervention: CHRs received a single oral dose of either 600mg of CBD (CHR-CBD) or a placebo (CHR-PLB). HCs were not given any drug. All participants were then studied using functional magnetic resonance imaging (fMRI) whilst performing a verbal learning task.

Main Outcomes and Measures: Brain activation during verbal encoding and recall, indexed using the blood-oxygen level-dependent haemodynamic response (BOLD) fMRI signal.

Results: Seventeen CHR-PLB [mean (SD) age= 25.35 (5.24) years; 10 females] and 16 CHR-CBD [mean (SD) age= 22.43 (4.95) years; 6 females] were compared with 19 HC [mean (SD) age= 23.89 (4.14) years; 8 females] participants. Brain activation (indexed using median sum of squares ratio of the BOLD effects model component to residual sum of squares) was analyzed from 16 CHR-PLB, 15 CHR-CBD and 19 HC. CHR-PLB had reduced activation relative to HC in the right caudate during encoding (CHR-PLB: median=-0.027, IQR= -0.041, -0.016; HC: median=0.020, IQR= -0.022, 0.056; $p<0.001$), and in the parahippocampal gyrus and midbrain during recall (CHR-PLB: median=0.002, IQR= -0.016, 0.010; HC: median=0.035, IQR= 0.015, 0.039; p=0.000096). Within these three regions, activation in the CHR-CBD was greater than in CHR-PLB, but lower than in HCs (parahippocampal gyrus/ midbrain- CHR-PLB: median=-0.007, IQR= -0.019, 0.008; CHR-CBD: median= -0.013, IQR= -0.027, 0.002; HC: median=0.034, IQR= 0.005, 0.059; $p<0.005$): the level of activation was thus intermediate to that in the other two groups. There were no significant group differences in task performance.

Conclusions and relevance: CBD may partially normalize alterations in parahippocampal, striatal and midbrain function associated with the CHR state. As they are critical to the pathophysiology of psychosis, the influence of CBD at these sites could underlie its therapeutic effects on psychotic symptoms.

Introduction

Epidemiological and clinical studies have implicated regular cannabis use as a risk factor for the development[1] of psychosis, and for poor clinical outcomes after its onset[2-4]. Psychosis is also associated with alterations in the endocannabinoid system (reviewed here[5,6]), independent of exposure to cannabis. The endocannabinoid system thus represents a potential therapeutic target for psychosis[7,8]. Its main central receptor, the CB1 cannabinoid receptor is ubiquitous in brain[9,10] and modulates the function of neurotransmitters, thought to be critically perturbed in psychosis, including dopamine and glutamate[11]. The constituent of cannabis responsible for its acute psychotomimetic effects[12-14] and its association with the development and relapse of psychosis is delta-9-tetrahydrocannabinol (THC)[1-4,15,16]. In contrast, Cannabidiol (CBD), one of the major non-psychoactive constituents of cannabis, has broadly opposite neural and behavioural effects[17-23]. In particular, we have shown that CBD has opposing effects to THC on activation in the striatum[17,18] during verbal memory and salience processing, on amygdala responses[17] during emotional processing, and on the functional connectivity[19] of these regions. Furthermore, pre-treatment with CBD blocks the experimental induction of psychotic symptoms by THC[17,20], and clinical studies indicate that CBD has antipsychotic and anxiolytic properties in patients with mental disorders ([24,25]also reviewed in[7,8]). CBD was non-inferior to antipsychotic medication in a 4-week clinical trial in first-episode psychosis[26], and improved psychotic symptoms when used as an adjunct to antipsychotic medicaton in a 6-week trial in patients with chronic psychosis[27].

Although there is good evidence that CBD can have beneficial effects on psychotic symptoms, how these effects are mediated in the brain remains unclear. The present study sought to address this issue by examining the effects of CBD in individuals at clinical high-risk for psychosis (CHR). CHR subjects typically experience clinically significant psychotic symptoms that are qualitatively similar to those seen in patients with frank psychosis[28], and are associated with high levels of distress[29]. Contemporary preclinical models propose that psychosis involves a perturbation of activity in the medial temporal lobe (MTL) that drives subcortical dopamine dysfunction through projections to the striatum and midbrain[30]. Moreover neuroimaging studies in CHR subjects indicate that the later onset of psychosis is linked to alterations in parahippocampal structure[31] and function[32-34] and to elevated striatal and midbrain dopamine activity.

In the present study, on the basis of previous studies, we expected that CHR subjects would display altered responses in the MTL, midbrain and striatum relative to HC. Our main hypothesis was that CBD would attenuate functional abnormalities in this triad of regions. While the MTL is critical for new learning[35], the midbrain[36-39] and striatum[39-43] also play a key role in supporting the encoding and updating of contextual information in memory. Therefore, we employed the verbal paired associate learning task (VPA), which engages these processes and brain regions[13,14]. Furthermore, transient psychotomimetic effects of THC have been related to its modulation of striatal[13] and midbrain[14] function and CBD[17] has been shown to oppose these striatal effects of THC during this task.

METHODS

Detailed methods are included as part of supplementary material (see eMethods and Figure S1A for CONSORT diagram). Thirty-three antipsychotic medication-naïve CHR participants[28] were recruited from early intervention services in the UK. Nineteen age-matched (± 3 years) healthy controls (HC) were recruited by local advertisement. All participants provided written informed consent. Individuals with history of previous psychotic or manic episode, neurological disorder or current DSM-IV diagnosis of substance dependence, IQ less than 70 and contraindication to MRI or treatment with CBD were excluded. Psychopathology was measured using Comprehensive Assessment of At-Risk Mental States (CAARMS; positive and negative symptoms)[28] and state-trait anxiety inventory- state subscale (STAI-S)[44] at baseline before drug administration. Two CHR participants were excluded, one from each of the CBD-treatment and placebo-treatment arms, after failing to correctly perform the imaging task, resulting in n=15 participants in the CHR-CBD group and n=16 in the CHR-PLB group.

Using a parallel-group, double-blind, placebo-controlled design, CHR participants were randomized to either CBD (CHR-CBD) or placebo (CHR-PLB) treatment and received a single oral dose of 600mg of CBD (THC-Pharm), a dose previously effective in established psychosis[26], or an identical placebo capsule respectively. Three hours after taking the CBD or placebo capsule, participants underwent functional magnetic resonance imaging (fMRI) whilst performing a VPA task that we have previously used in conjunction with fMRI and pharmacological challenge[13,14], including CBD administration[17] (see eMethods for

justification of CBD dose and time of fMRI scanning, and Figure S1B for CBD plasma levels). HC participants were investigated under identical conditions, but did not receive any study drug.

All participants were asked to have refrained from cannabis for 96 hours, alcohol for a minimum of 24 and nicotine for 6 hours before scanning and any other recreational drugs for two weeks before the study day. A urine sample prior to scanning was used to screen for use of illicit drugs.

The VPA task (described in detail in eMethods) comprised 3 conditions (encoding, recall, and baseline), with stimuli presented visually in blocks and accuracy of responses recorded online. During encoding, participants were shown word-pairs and asked to say 'yes' or 'no' aloud after each pair to indicate whether they went well together. The same word pairs were presented in the encoding condition 4 times, so that the associations could be learned over repeated blocks. During recall, one of the words from previously presented pairs was shown and participants were asked to say the word that it had previously been associated with. Subjects said "pass" if they could not recall the missing word. During baseline, participants viewed a pair of blank blue rectangles of identical dimensions as in the encoding/ recall condition.

For each participant, the blood oxygen level–dependent haemodynamic (BOLD) response of the brain during each encoding and recall block, measured using a 3T MRI scanner (gradient echo sequence axially; 39 x 3mm slices, 3.3mm slice gap; 30ms echo time; compressed acquisition with a 2s repetition time and 3s silence), was contrasted with that during the baseline condition.

Analysis | fMRI data were analyzed with software developed at the Institute of Psychiatry, Psychology and Neuroscience (XBAM, version 4.1), using a nonparametric approach to minimize assumptions (https://www.kcl.ac.uk/ioppn/depts/neuroimaging/research/imaginganalysis/Software/XBAM.aspx)[45,46].

Images were corrected for motion[47], spatially smoothed and the experimental design was convolved with two gamma-variate functions to model the BOLD response. Using the constrained BOLD effects model, a best fit between the weighted sum of these convolutions and the change over time at each voxel was computed[48]. Following least-squares fitting of this model to the time series at each voxel, a sum of squares (SSQ) ratio statistic (ratio of the model component to residual sum of squares) was estimated for the encoding and recall

conditions relative to baseline. Significance of the estimated SSQ values at each voxel was determined by permutation tesing[49,50]. SSQ ratio maps for each individual were transformed into standard stereotactic space[51,45] and group activation maps were computed for each group in each drug condition by determining the median SSQ ratio at each voxel (over all individuals) in the observed and permuted data maps. Group activation maps for each condition were compared against each other (CHR-PLB vs HC and CHR-CBD vs CHR-PLB) using non-parametric repeated-measure analysis of variance (ANOVA)[45]. The voxel-wise statistical threshold was set at p=0.05 and the cluster-wise thresholds were adjusted to ensure that the number of false positive clusters per brain would be <1 (regions that survived this critical statistical threshold and the corresponding p values are reported).

The BOLD response in each subject was modelled using only trials associated with correct responses in the recall condition. To test the hypothesis that activation in the CHR-CBD group would be intermediate between that of HC and CHR-PLB subjects we examined whether a linear relationship in brain activation (CHR-PLB > CHR-CBD > HC or CHR-PLB < CHR-CBD < HC) existed within the whole brain.

Recall performance was analysed using repeated-measures analysis of variance. Correlational analysis between recall score and brain activation was conducted using Pearson's test (two-tailed).

RESULTS

There were no significant group differences between the CHR-PLB and HC and CHR-PLB and CHR-CBD groups in demographic and clinical variables, except that the CHR-PLB group had fewer years of education than the HC group (Table 1).

fMRI results

Main effects of encoding and recall in healthy controls

In HC, relative to the baseline condition, the encoding condition was associated with activation in the left anterior cingulate cortex, the right caudate, the left precentral gyrus, and the cuneus (eTable 1). The recall condition relative to the baseline condition was associated with activation in the left parahippocampal and left

transverse temporal gyri, and decreased activation in the left middle occipital, the right lingual and inferior frontal gyri (eTable 2).

Differences in activation associated with the CHR state (CHR-PLB vs HC)

Encoding | During the encoding condition, CHR-PLB participants showed greater activation than HC in the right middle frontal gyrus and adjacent parts of the inferior frontal gyrus and insula; the left insula/ claustrum and adjacent inferior frontal gyrus and putamen; the right precentral gyrus and adjacent postcentral gryus and inferior parietal lobule; and the left cerebellum and adjacent lingual gyrus (Table 1, Figure 1A). Relative to CHR-PLB, HC showed greater activation in the right subcallosal gyrus/ caudate head; the left anterior cingulate; the right caudate tail extending to the posterior cingulate cortex; and in the right precuneus and cuneus (Table 2A, Figure 1A).

Recall | During the recall condition, the CHR-PLB participants showed greater activation than HC in clusters encompassing the right inferior frontal, middle frontal and precentral gyri, and insula; the right cuneus, fusiform, lingual gyri and posterior cingulate gyri; and the left cerebellum and middle occipital and fusiform gyri (Table 2B, Figure 1B). HC showed greater activation in four clusters in the left hemisphere: these involved the parahippocampal gyrus, midbrain, cerebellum and thalamus; superior temporal and middle temporal gyri; superior and transverse temporal gyri; and middle frontal gyrus (Table 2B, Figure 1B).

Effect of CBD on activation in CHR participants (CHR-PLB vs CHR-CBD)

Encoding | During the encoding condition, the CHR-PLB group showed greater activation than the CHR-CBD group in a cluster in the left parahippocampal gyrus that extended into the superior temporal gyrus and cerebellum, but less activation in the precentral gyri (Table3A, Figure 1C).

Recall | During the recall condition, the CHR-PLB showed less activation than the CHR-CBD group in three clusters, with foci in the left cingulate gyrus and adjacent body of caudate; the right precentral gyrus, extending

to the cingulate gyrus; and in the medial frontal gyrus (Table 3A, Figure 1D). There were no clusters of greater activation in the CHR-PLB than the CHR-CBD group.

Between-group linear analysis

This analysis identified clusters where there was a linear pattern of activation across the 3 groups, such that activation in the CHR-CBD group was intermediate to that in the CHR-PLB and HC groups.

Encoding | There were 7 clusters where encoding-related engagement was greatest in the CHR-PLB group, lowest in the HC group, and at an intermediate level in the CHR-CBD group. These involved the right inferior frontal and middle frontal gyri and insula; left insula and putamen; 3 clusters in the precentral gyri; right fusiform gyrus and adjacent cerebellum; left cerebellum and fusiform gyrus (Table 3B, Figure 2A-B; Also see supplementary figure S2A displaying all regions). The right inferior frontal gyrus, left insula and precentral clusters overlapped with the regions where the CHR-PLB showed increased activation during encoding relative to the HC group in the earlier paired comparison.

There were 4 clusters where there was a linear between-group relationship in the opposite direction (CHR-PLB< CHR-CBD<HC). These involved the left caudate head and putamen and anterior cingulate cortex; right subcallosal gyrus and caudate head; tail of the right caudate and adjacent posterior cingulate cortex; and the precuneus and right cuneus. In these clusters, activation during encoding was greatest in the HC group, lowest in the CHR-PLB group, and at an intermediate level in the CHR-CBD group (Table 3B, Figure 2A-B; Also see supplementary figure S1A displaying all regions). All 4 clusters overlapped with clusters where HC had shown greater activation than the CHR-PLB group during encoding in the previous paired comparison.

Recall | In 3 clusters, recall-related engagement was greatest in the CHR-PLB participants, and lowest in HC, and at an intermediate level in the CHR-CBD participants. These clusters comprised the right inferior frontal gyrus extending to ipsilateral middle frontal gyrus and insula; precuneus extending to cuneus, lingual, middle

occipital and fusiform gyri and cerebellum on the right side; and cerebellum extending to fusiform, lingual and inferior occipital gyri on the left side (Table 3C, Figure 2C-D; Also see supplementary figure S2B displaying all regions). All 3 clusters overlapped with clusters where the CHR-PLB had shown greater activation than HC during recall in the paired comparison.

Conversely, there were 4 clusters where activitation was greatest in the HC group, lowest in the CHR-PLB group and at an intermediate level in the CHR-CBD participants. These included the left parahippocampal gyrus, midbrain and cerebellum; left thalamus; the left transverse temporal gyrus extending to superior temporal gyrus; and the left precentral and cingulate gyri and caudate body (Table 3C, Figure 2C-D; Also see supplementary figure S2B displaying all regions). The left parahippocampal gyrus and transverse temporal gyrus clusters overlapped with clusters where HC had shown greater activation than CHR-PLB participants during recall in the paired group comparison.

Relationship between recall performance and brain activation:

Across all participants, total recall score was directly correlated (r=0.28, p=0.046) with the level of left parahippocampal activation during recall. See eResults for exploratory analyses examining relationship between brain activation and symptoms.

DISCUSSION

As expected and in line with data from previous neuroimaging comparisons of CHR subjects and controls[52-54], we found that under placebo conditions, CHR participants showed differential activation relative to controls in several regions. These regions of differential response included the three areas thought to be critical to the pathophysiology of the CHR state, the striatum (during verbal encoding), and the MTL and midbrain (during verbal recall).

To test our main hypothesis, we identified regions where there was a linear pattern of activation across the three subject groups, such that the level of activation in CHR subjects given CBD was intermediate to that in the CHR-placebo and control groups. We found that this pattern of differential activation was evident in the striatum during encoding, and in the parahippocampal

cortex and midbrain during recall. Moreover, these regions of differential activation overlapped with the areas where CHR participants under placebo conditions had shown altered activation in the paired comparison with the controls. These findings suggest that during verbal encoding, the administration of a single dose of CBD attenuated the reduction in the striatal response that evident in CHR participants relative to controls under placebo conditions. Similarly, administration of CBD appeared to attenuate the reduction in the parahippocampal and midbrain responses during verbal recall that was seen in CHR participants under placebo conditions relative to controls. Although this interpretation is cautious because the findings are based on cross-sectional as opposed to within-subject comparisons, these data suggest that in these regions, CBD may partially normalise responses to verbal encoding and recall in CHR subjects. As there were no significant differences in memory performance, this differential activation was not attributable to differential task performance.

Acute effects of CBD on responses in these areas in CHR participants are consistent with previous data from two studies that used a single dose of CBD in healthy volunteers. These studies indicated that in controls, CBD augmented parahippocampal and striatal activation[17,18] during the same learning task[17] as used in the present study and had a similar effect on parahippocampal and striatal responses during an attentional salience task[18]. In both of these studies, the administration of a single dose of THC induced transient psychotic symptoms, and the effect of THC on parahippocampal and striatal activation was the opposite to that of CBD.

Preclinical models suggest that overactivity in the MTL region drives subcortical dopamine dysfunction through projections to the striatum and midbrain[55,56]. Moreover, neuroimaging studies in CHR subjects indicate that the subsequent onset of psychosis is linked to alterations in MTL structure[31] and function[32,34], and to elevated striatal and midbrain dopamine function[57-59]. Effects of CBD on parahippocampal, striatal and midbrain function in CHR participants are thus of particular interest as these areas may play a critical role in the pathophysiology of psychosis[30]. A partial normalization of dysfunction in these regions could contribute to the therapeutic effects of CBD that have been reported in patients with psychosis[26,27] and anxiety disorders[25].

The molecular mechanism of action that may underlie the effects of CBD in CHR patients is unclear. CBD has effects on a number of signaling pathways[11,60,61], including on the CB1 receptors [62,63] and may modulate glutamatergic neurotransmission particularly in the hippocampus through multiple pathways[64-66] and striatal glutamatergic and CB1 receptor expression[67]. In patients with psychosis, the effects of CBD on psychotic symptoms have been related to its influence on levels of the endogeneous cannabinoid anandamide[26]. Future studies therefore need to investigate the neurochemical and receptor level mechanisms that may underlie the antipsychotic effects of CBD.

Across all participants, the level of activation in the left parahippocampal cortex during verbal recall was directly correlated with total recall score during the task, consistent with the key role of this region in relational memory binding and retrieval [68,69] and in supporting association-based recall[70]. Attenuated parahippocampal engagement in CHR-PLB is consistent with meta-analytic and independent evidence from studies in patients with established psychotic disorders such as schizophrenia[71-73] and in studies in those at clinical[34,74] and familial/ genetic[73,75] risk of psychosis. Further discussion of the results is presented as supplementary material (see eDiscussion 1).

Limitations

Our results need to be considered in light of certain caveats including related to study design (see eDiscussion 2).

Conclusions

This study suggests that a single dose of CBD in an experimental setting may partially normalise dysfunction in the MTL, striatum and midbrain in subjects at CHR for psychosis. It would be useful to now investigate whether similar modulatory effects are evident in patients who have received a course of treatment with CBD in a clinical setting.

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Contributors

SB and PM designed the study; SB supervised the collection (RW, EAK) and analysis (AON) of the data and wrote the first draft of the paper. All authors contributed to the interpretation of the data, revised the manuscript and have approved the final manuscript.

Access to Data and Data Analysis: Sagnik Bhattacharyya had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest disclosures

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Tables:

Table 1. Sociodemographic and clinical measures at baseline

	HC (n=19) [a]	CHR-PLB (n=17)	CHR-CBD (n=16)	*Statistics*
Age (years), mean±SD	23.89±4.14	25.35±5.24	22.43±4.95	HC vs CHR-PLB: *p*= 0.36 CHR-PLB vs CHR-CBD: *p*= 0.11
Gender (m: f)	16:8	7:10	10:6	HC vs CHR-PLB: *p*= 0.50 CHR-PLB vs CHR-CBD: *p*= 0.30
Education (years), mean±SD	16.94±1.59	12.00±3.69	14.50±3.06	HC vs CHR-PLB: *p*= 0.01 CHR-PLB vs CHR-CBD: *p*= 0.15
CAARMS positive symptoms	-	42.94±29.46	40.19±20.79	*p*= 0.75
CAARMS negative symptoms	-	28.41±20.49	23.25±16.49	*p*= 0.43
STAI-S	-	38.94±10.17	40.31±9.06	*p*= 0.68
Number of patients who made a transition to psychosis (n)	-	1	1	*p= 1*
Urine Drug screen (UDS) results: Clean	- [b]	8	10	*CHR-PLB vs CHR-CBD: p=0.45*
THC	-	5	2	
Morphine	-	0	1	
Benzodiazepines	-	1	0	
PCP	-	1	0	
Missing	-	2	3	
Cannabis Use: Lifetime use (Current use) (n)	- [c]	17 (7)	15 (7)	*Lifetime use: p=0.48; Current use: p=1*
Cannabis Use: Frequency- More than once a week	-	12	11	*p=0.38*
Once/ twice monthly	-	3	1	
Few times a year	-	0	2	
Only once/ twice lifetime	-	2	1	
Alcohol Use: Lifetime use (Current use) (n)	- [d]	13 (10)	12 (11)	*Lifetime use: p=1; Current use: p=0.59*
Alcohol Use: Frequency- Daily	-	2	1	*p=0.59*
More than once a week	-	4	4	
Few times a month	-	3	4	
Few times a year	-	2	3	
Only once/ twice lifetime	-	2	0	
Nicotine Use: Lifetime use (Current use) (n)	- [e]	7 (5)	11 (9)	*Lifetime use: p=0.16; Current use: p=1*
Nicotine Use: Frequency- Daily	-	6	8	*p=0.68*
More than once a week	-	1	2	
Few times a month	-	0	1	
Total recall score	29.74±2.51	27.62±4.42	28.31±2.91	$F_{2,48}$=1.84, p=0.17

[a-] HC were selected to have minimal drug use and hence not compared with CHR groups on these parameters

[b-] HC tested negative on UDS for all substances tested.

[c-] Cannabis use < 10 times lifetime (no current users).

[d-] Alcohol use: Lifetime users-13; Frequency (More than once a week- 5; Few times a month- 3; Few times a year- 4)

[e-] Nicotine use: Lifetime users-5 (2 current users); Frequency (Daily-2; Few times a month- 1; Few times a year- 1; Only once/ twice lifetime- 1)

Table 2 A: Differences in activation between placebo-treated CHR (CHR-PLB, n=16) participants and healthy controls (HC, n=19) during verbal encoding

CHR-PLB > HC					
Region	**Coordinates of peak (TAL)**			**Cluster size**	**p value***
	X	**Y**	**Z**		
Middle frontal gyrus extending to inferior frontal gyrus and insula	36	37	10	165	0.0001
Claustrum/ Insula extending to inferior frontal gyrus and putamen	-25	26	3	96	0.001
Precentral gyrus extending to postcentral gyrus and inferior parietal lobule	40	-7	36	134	0.00051
Left cerebellum extending to lingual gyrus	-40	-67	-16	77	0.0011
CHR-PLB < HC					
Subcallosal gryus / caudate head	14	11	-10	72	0.00093
Anterior cingulate	-4	41	0	18	0.00093
Caudate tail extending to posterior cingulate cortex	18	-33	16	28	0.00021
Precuneus extending to cuneus	4	-63	30	156	0.00021

TAL = Talairach coordinate system. *Corrected for less than 1 false positive cluster.

Table 2B: Differences in activation between placebo-treated CHR (CHR-PLB, n=16) participants and healthy controls (HC, n=19) during verbal recall

CHR-PLB > HC					
Region	**Coordinates of peak (TAL)**			**Cluster size**	**p value***
	X	**Y**	**Z**		
Inferior frontal gyrus extending to middle frontal gyrus, insula and precentral gyrus	47	11	23	146	0.0001
Cuneus extending to fusiform gyrus, lingual gyrus and posterior cingulate cortex	29	-74	7	196	0.0001
Cerebellum extending to middle occipital gyrus and fusiform gyrus	-36	-63	-13	83	0.0015
CHR-PLB < HC					
Parahippocampal gyrus extending to midbrain, cerebellum and thalamus	-18	-26	-13	131	0.000096
Superior temporal gyrus extending to the middle temporal gyrus	-50	-18	0	80	0.00038
Superior temporal gyrus extending to the transverse temporal gyrus	-50	-30	13	33	0.003
Middle frontal gyrus	-25	11	33	57	0.0034

TAL = Talairach coordinate system. *Corrected for less than 1 false positive cluster.

Table 3A: Differences in activation between placebo-treated CHR (CHR-PLB, n=16) and CBD-treated CHR (CHR-CBD, n=15) subjects during verbal encoding and recall

Region	**Coordinates of peak (TAL)**			**Cluster size**	**p value***
	X	**Y**	**Z**		
Encoding: CHR-PLB > CHR-CBD					
Parahippocampal gyrus, extending to superior temporal gyrus and cerebellum	-29	-30	-13	75	0.0032
Encoding: PLB-CHR < CBD-CHR					
Precentral gyrus	43	-7	30	40	0.0033
	-40	-11	36	72	0.0005
Recall: PLB-CHR < CBD-CHR					
Cingulate gyrus, extending to body of caudate	-14	15	30	365	0.00010
Precentral gyrus, extending to cingulate gyrus	43	-18	33	362	0.00010
Medial frontal gyrus	-7	0	49	61	0.0021

TAL = Talairach coordinate system. *Corrected for less than 1 false positive cluster.
There were no significant clusters for **PLB-CHR > CBD-CHR** during recall.

Table 3B: Linear relationship in activation across all groups during verbal encoding (CHR-PLB, n=16; CHR-CBD, n=15; HC, n=19)

Region	**Coordinates of peak (TAL)**			**Cluster size**	**p value***
	X	**Y**	**Z**		
CHR-PLB > CHR-CBD > HC					
Inferior frontal gyrus, extending to middle frontal gyrus and insula	40	37	10	135	0.0001
Insula, extending to putamen	-36	11	10	112	0.0004
Precentral gyrus	-40	-11	30	39	0.0040
	-51	-4	16	34	0.0031
	40	-11	36	124	0.0002
Fusiform gyrus, extending to cerebellum	43	-44	-13	53	0.0027
Cerebellum, extending to fusiform gyrus	-22	-52	-16	100	0.0004
CHR-PLB < CHR-CBD < HC					
Caudate head, extending to anterior cingulate and putamen	-14	22	0	44	0.0041
Subcallosal gyrus/ caudate head	14	11	-10	87	0.0011
Caudate tail, extending to posterior cingulate cortex	18	-37	13	65	0.0038
Precuneus, extending to Cuneus	4	-63	30	185	0.0001

TAL = Talairach coordinate system. *Corrected for less than 1 false positive cluster.

Table 3C: Linear relationship in activation across all groups during verbal recall (CHR-PLB, n=16; CHR-CBD, n=15; HC, n=19)

Region	Coordinates of peak (TAL)			Cluster size	p value*
	X	Y	Z		
CHR-PLB > CHR-CBD > HC					
Inferior frontal gyrus, extending to middle frontal gyrus and insula	47	11	23	120	0.0001
Precuneus, extending to cuneus, lingual, middle occipital and fusiform gyri and cerebellum	25	-74	7	176	0.0001
Cerebellum, extending to fusiform, lingual and inferior occipital gyri	-36	-63	-13	73	0.0019
CHR-PLB < CHR-CBD < HC					
Parahippocampal gyrus, extending to midbrain and cerebellum	-18	-26	-13	82	0.0008
Thalamus	-7	-26	-3	33	0.0032
Transverse temporal gyrus, extending to superior temporal gyrus	-50	-26	13	33	0.0037
Precentral gyrus, extending to cingulate gyrus and body of caudate	-36	18	36	60	0.0016

TAL = Talairach coordinate system. *Corrected for less than 1 false positive cluster.

Figure Legends:

Figure 1. Altered brain activation in CHR (CHR-PLB vs HC)

A. Clusters showing greater (red/yellow) or reduced (blue/ green) activation in CHR-PLB compared to HC during the encoding condition.

B. Clusters showing greater (red/yellow) or reduced (blue/ green) activation in CHR-PLB compared to HC during the recall condition.

C. Clusters showing greater (red/yellow) or reduced (blue/ green) activation in CHR-PLB compared to CHR-CBD during verbal encoding.

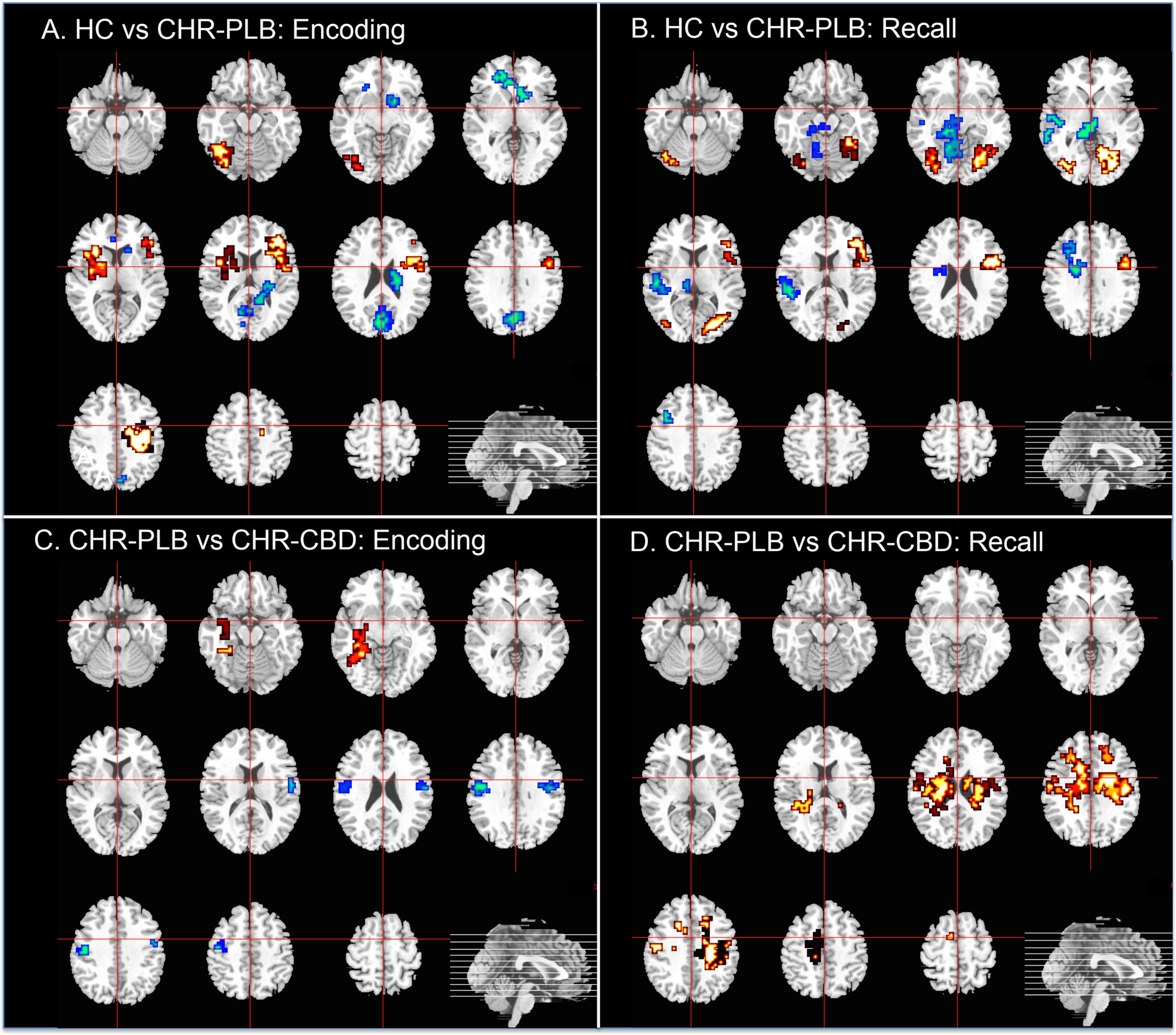
D. Clusters showing greater (red/yellow) activation in CHR-PLB compared to CHR-CBD during the recall condition.

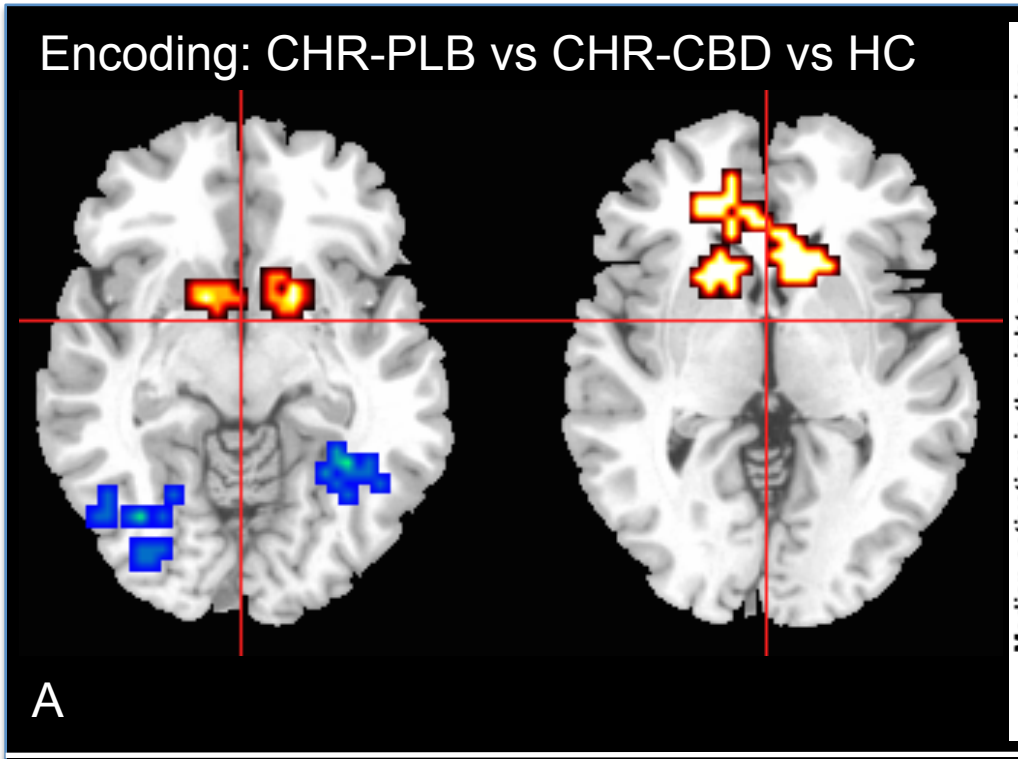
The right side of the brain is shown on the right of the images.

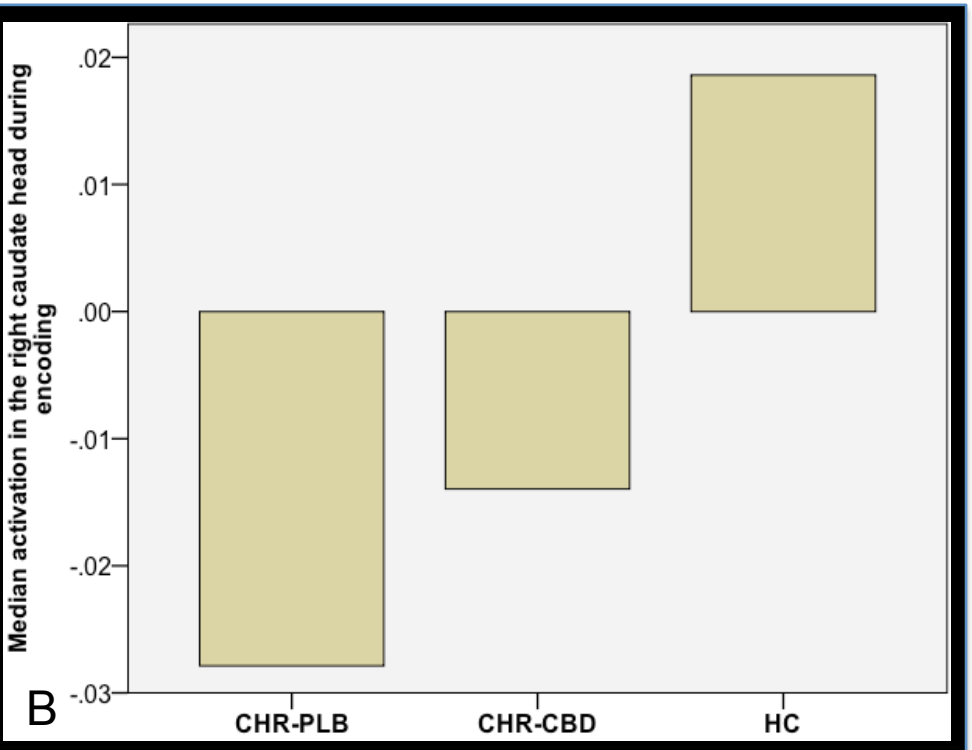
Figure 2. Effect of CBD on brain activation compared to placebo in CHR and healthy controls

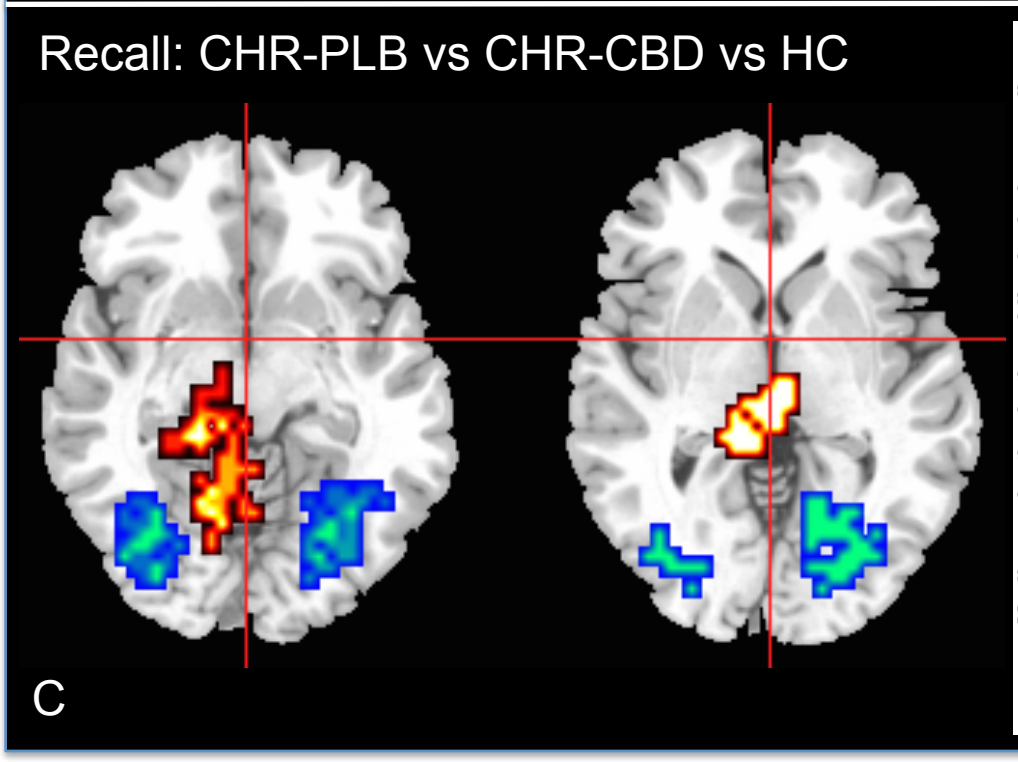
A. Clusters where activation during encoding differed across the 3 groups in a linear relationship. In the head of caudate (red/yellow), activation was greatest in HC, lowest in CHR-PLB and intermediate in CHR-CBD. The opposite pattern (CHR-PLB>CHR-CBD>HC) was seen in occipital regions (blue).
B. Activation in each group in the right caudate head during encoding (arbitrary units; as indexed using median SSQ ratio)
C. Clusters where there was a linear group difference in activation during recall. In the parahippocampal region and midbrain (red/yellow), activation was greatest in HC, lowest in CHR-PLB and intermediate in CHR-CBD. The opposite pattern (CHR-PLB>CHR-CBD>HC) was seen in occipital regions (blue).
D. Median activation in each group in the midbrain during recall (arbitrary units; as indexed using median SSQ ratio)

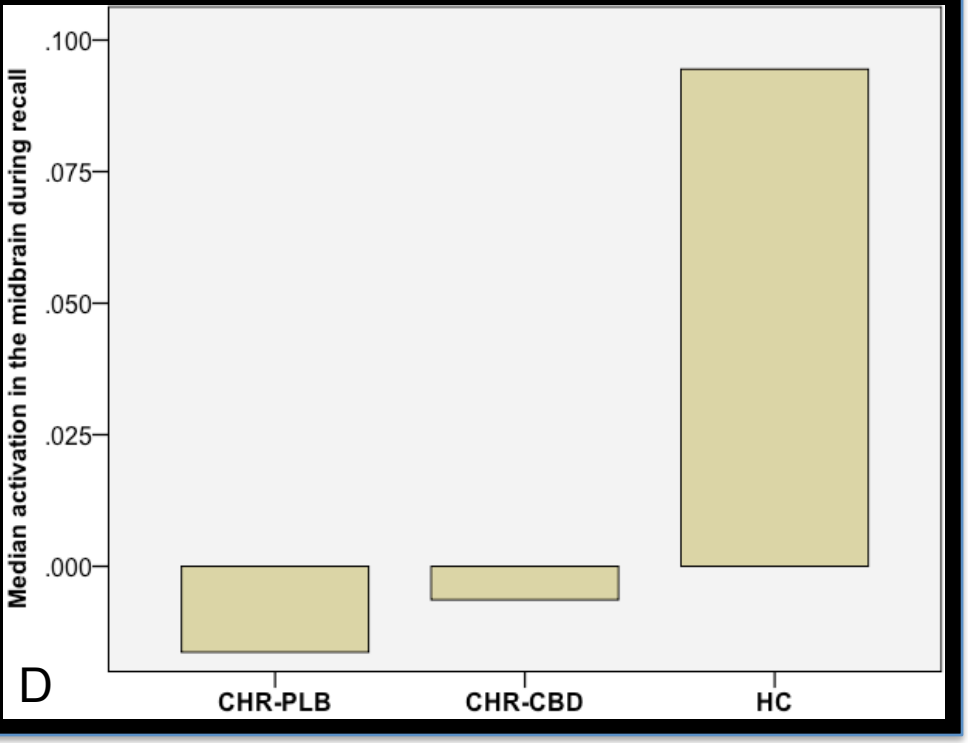
SSQ ratio statistic refers to the ratio of sum of squares (SSQ) of deviations from the mean image intensity due to the model (over the whole time series), to the SSQ of deviations due to the residuals. The right side of the brain is shown on the right of the images.


A. HC vs CHR-PLB: Encoding
B. HC vs CHR-PLB: Recall
C. CHR-PLB vs CHR-CBD: Encoding
D. CHR-PLB vs CHR-CBD: Recall


Encoding: CHR-PLB vs CHR-CBD vs HC
A


Median activation in the right caudate head during encoding
.02
.01
.00
-.01
-.02
-.03
CHR-PLB
CHR-CBD
HC
B


Recall: CHR-PLB vs CHR-CBD vs HC
C


Median activation in the midbrain during recall
.100
.075
.050
.025
.000
CHR-PLB
CHR-CBD
HC
D